CDEC FINAL RECOMMENDATION

RANIBIZUMAB
(Lucentis — Novartis Pharmaceuticals Canada Inc.)
Indication: Choroidal Neovascularization Secondary to Pathologic Myopia

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that ranibizumab be listed for the treatment of visual impairment due to choroidal neovascularization secondary to pathologic myopia, if the following condition is met:

Condition:
- Overall drug plan costs for ranibizumab should not exceed those currently allocated to verteporfin photodynamic therapy (vPDT) for patients with pathologic myopia and choroidal neovascularization.

Reasons for the Recommendation:
1. One 12-month, double-blind randomized controlled trial (RCT) (RADIANCE; N = 277) demonstrated that treatment with ranibizumab resulted in a statistically significant improvement in best corrected visual acuity (BCVA) compared with vPDT; however, the clinical significance of this difference is uncertain as it did not exceed the minimal clinically important difference (MCID) for this end point.
2. At the submitted price ($1,575.00 per vial), ranibizumab has a lower acquisition cost than verteporfin ($1,704.00) and the administration of ranibizumab ($105 per intravitreal injection) costs less than photodynamic therapy ($330); however, overall treatment costs with ranibizumab could exceed those of vPDT if the mean number of injections per patient exceeds 4.5 in the first year.

Of Note:
- CDEC noted that ranibizumab treatment requires administration by a qualified ophthalmologist experienced in intravitreal injections.
- Due to the variability of use within the RADIANCE trial, there was insufficient evidence for CDEC to recommend a specific number of vials to which the drug plans participating in the CADTH Common Drug Review (CDR) should limit coverage of ranibizumab.

Background:
Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds human vascular endothelial growth factor A (VEGF-A) and suppresses neovascularization. Ranibizumab is indicated for the treatment of visual impairment due to choroidal neovascularization secondary to pathologic myopia; neovascular (wet) age-related macular degeneration; visual impairment due to macular edema secondary to retinal vein occlusion; and visual impairment due to diabetic macular edema.

Ranibizumab is supplied as a 10 mg/mL solution in single-use vials for intravitreal injection. For the treatment of choroidal neovascularization secondary to pathologic myopia, the product monograph recommends that treatment be initiated with a single 0.5 mg injection. If monitoring reveals signs of disease activity (e.g., reduced visual acuity [VA] and/or signs of lesion activity), further treatment is recommended.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of ranibizumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals with choroidal neovascularization.

Patient Input Information
The following is a summary of information provided by two patient groups that responded to the CDR call for patient input:

- Because of its prevalence among people of working age, the central vision loss affects a patient's career, independence, family dynamics, responsibilities, and quality of life. Patients may lose their ability to complete daily activities and become reliant on the assistance of caregivers to attend medical appointments, prepare meals, go shopping, and participate in social activities. Depression can also set in due to the reduction or loss of independence, the actual or potential loss of employment, the loss of driving privileges, and the fear of a life with little or no vision. Patients also become more susceptible to falls.
- Caregivers have to deal with all the emotional effects of vision loss in someone who had been previously independent. They must provide a safe physical environment for the patient. They may be required to take time off work to transport patients and to perform or help with a variety of household tasks.
- Patients expect this new treatment, which many have heard about because of its use by patients with other ocular conditions, to allow them to recover some of their VA; they are willing to tolerate mild side effects to regain sight or prevent further vision loss.

Clinical Trials
The CDR systematic review included one phase 3, double-blind, multi-centre, active-controlled RCT (RADIANCE; N = 277). Study participants were randomized (2:2:1) to one of the following three treatment groups: Group I received 0.5 mg ranibizumab on day 1 and one month later; thereafter, patients were re-treated following a decrease of VA; Group II received 0.5 mg ranibizumab on day 1 and were re-treated thereafter based on disease activity; and Group III received vPDT on day 1 and were eligible to receive 0.5 mg ranibizumab after three months following disease activity. Sham vPDT and sham injections (needle-free syringe) were used to preserve masking.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- BCVA measured with Early Treatment Diabetic Retinopathy Study (ETDRS) letters — ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows. ETDRS was assessed using the following:
  - Difference from baseline of the average level of BCVA over all monthly post-baseline assessments from months 1 to 3 and 1 to 6
  - Proportion of patients who gained 15 letters (or 10 letters) or reached the 84-letters threshold at months 3, 6, and 12
  - Proportion of patients who lost 15 letters (or 10 letters) at months 3, 6, and 12
  - Change from baseline at months 3, 6, and 12
- Change from baseline in central retinal thickness at months 3, 6, and 12
- National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) — a 25-item questionnaire that assesses 11 vision-related constructs, in addition to a single-item general health component. The possible range of the NEI-VFQ-25 total score is between 0 (worst possible) and 100 (best possible).
- Euro Quality of Life Questionnaire-5 Domains (EQ-5D) — a generic quality of life instrument consisting of five dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and a visual analogue scale for rating health today. Weighted scoring produces an EQ-5D index score, with a higher score indicating better general health.
- Work Productivity and Activity Impairment: General Health Questionnaire (WPAI:GH) — six items related to current employment status, the number of hours worked and missed from work, and the extent to which productivity and the ability to perform regular daily activities has been affected by health problems over the past seven days.
- Total adverse events, serious adverse events, withdrawals due to adverse events, and notable harms.

The primary objective of RADIANCE was to assess whether ranibizumab was superior to vPDT for improving BCVA in ETDRS letters after three months. The key secondary objective was to compare the two ranibizumab treatment regimens (Group I and Group II) for non-inferiority based on BCVA after six months.

Efficacy

- After three months, the average improvement in BCVA compared with baseline was 11 letters in ranibizumab-treated patients versus two letters in vPDT-treated patients. The difference in the improvement in BCVA for Group I and Group II versus the vPDT group (Group III) was 8.5 (95% confidence interval [CI], 5.8 to 11.2; $P < 0.00001$) and 8.6 (95% CI: 6.1 to 11.1; $P < 0.00001$) letters, respectively. Those differences were slightly lower than the MCIDs suggested in the literature (10 to 15 letters).
- A greater proportion of ranibizumab-treated patients (range: 62% to 66%) gained at least 10 ETDRS letters (or reached a BCVA of 84 letters) compared with vPDT-treated patients (27%).
- After six months, the difference between the two ranibizumab treatment groups was 0.1 letters (95% CI: –2.2 to 2.0), which was below the non-inferiority margin of five letters. This suggested that both ranibizumab treatment regimens were similarly efficacious.
- Central retinal thickness decreased by 61 µm to 78 µm in ranibizumab-treated patients compared with a decrease of 12 µm in vPDT-treated patients.

- Visual function assessed using the NEI-VFQ-25 suggested that the improvement from baseline due to ranibizumab treatment (a 4- to 5-point improvement) exceeded the 4-point MCID, whereas no meaningful improvement was observed in the vPDT-treated group (0.3 point improvement).
- Changes in the EQ-5D and WPAI:GH scores were highly variable and inconsistent among treatment groups, and therefore no conclusions could be made regarding the relative efficacy of ranibizumab versus vPDT for these outcomes.
- After 12 months, the mean number of ranibizumab injections per patient was greater in Group I (4.6) than in Group II (3.5).

Harms (Safety and Tolerability)

- Serious adverse events were reported for 5% of ranibizumab-treated patients and 0% of vPDT-treated patients.
- The proportion of patients who experienced at least one ocular adverse event ranged from 37% to 43% in all patients who received ranibizumab compared with 27% for those treated with vPDT alone. The most commonly reported ocular adverse events in ranibizumab-treated patients were conjunctival hemorrhage (5.3% to 11.3%), punctate keratitis (2.5% to 7.5%), and increased intraocular pressure (2.8% to 10.5%), none of which occurred in vPDT-treated patients. Non-ocular adverse events were also more commonly reported for patients who received ranibizumab (range: 43% to 50%) compared with patients who did not receive ranibizumab (33%).
- There were no withdrawals due to adverse events reported in any of the treatment groups in RADIANCE.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing ranibizumab (one injection with retreatment as needed based on disease activity) versus vPDT over a patient lifetime horizon, from a public payer perspective. VA data from RADIANCE, the Verteporfin in Photodynamic Therapy (VIP) study, and observational data were used to inform the model. Using observational data, each VA health state was assigned a utility value and health care costs, as well as a mortality risk.

In the manufacturer's base-case analysis, ranibizumab was dominant over vPDT (i.e., less costly [savings of $1,808] and of greater clinical benefit [gain of 0.55 quality-adjusted life-years]). There were a number of parameters in the model associated with uncertainty, specifically regarding the frequency and incremental benefits of ranibizumab, as well as the clinical course of choroidal neovascularization. Under conservative assumptions regarding the clinical benefit of ranibizumab compared with vPDT (i.e., no clinical difference), ranibizumab remained cost saving.

Whether ranibizumab is cost saving, and the extent of the cost savings, is dependent on the frequency of ranibizumab dosing in actual practice as well as the cost of drug therapy. The manufacturer assumed the following treatment frequencies:

- Ranibizumab would be administered a mean of 3.5 times in the first year, once in the second year, followed by no treatment.
- vPDT would be performed a mean of 3.4 times in the first year, 1.7 times in the second year, followed by no treatment.

Sensitivity analyses varying the dosing frequency resulted in ranibizumab being more costly than vPDT when at least one additional injection of ranibizumab is required beyond what was assumed by the manufacturer in the first year (i.e., a mean of ≥ 4.5 rather than 3.5 injections). While the drug and administration costs are favourable for ranibizumab (drug $1,575; intravitreal injection $105) compared with vPDT (drug $1,704; PDT $330), ranibizumab becomes more expensive if incremental drug or administration costs are modified (for example, a price reduction for verteporfin ≥ 20%).

Given the lower drug acquisition and administration costs for ranibizumab ($1,680 per treatment) compared with vPDT ($2,034 per treatment), ranibizumab remains cost saving if observed VA differences do not result in clinical or subsequent health care cost differences. In this cost-minimization scenario, ranibizumab becomes more costly if it is used with greater frequency, or if the cost of verteporfin is 20% less than the price suggested by the manufacturer.

Other Discussion Points:
CDEC noted the following:

- Coverage for verteporfin for choroidal neovascularization secondary to pathologic myopia varies across the CDR-participating drug plans. In some jurisdictions, verteporfin is covered but administered in hospital settings and is therefore not listed as an insured benefit on public drug plans.
- Only a single eye was treated in RADIANCE.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- The long-term comparative efficacy of ranibizumab compared with vPDT could not be determined from the 12-month double-blind phase of RADIANCE; however, observational data favoured ranibizumab over vPDT at 24 months.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 21, 2015 Meeting

Regrets:
One CDEC member was unable to attend this portion of the meeting.

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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